Sport-Caught Fish and Breast Cancer

Angling for More Data

Not-so-great lakes? New research raises concerns that sport-caught lake fish may contribute to high contaminant exposures in women who eat it, with potential risks for breast cancer.

The U.S. Food and Drug Administration inspects fish sold at market for environmental contaminants and removes tainted seafood from sale. But consumption of sport-caught fish by fishing enthusiasts and those with whom they share their catch may expose these people to chemicals that affect development of breast cancer in some women, according to a study by University of Wisconsin Comprehensive Cancer Center staff scientist Jane McElroy and colleagues [*EHP* 112:156–162].

Despite advisories warning anglers away from contaminated fishing spots, consumption of sport-caught fish remains an important route of human exposure to halogenated hydrocarbons thought to be risk factors for breast cancer. Several of these agents—including polychlorinated biphenyls (PCBs), oily liquids not manufactured since the 1970s but once used as industrial lubricants and coolants; the U.S.–banned pesticide DDT and its most stable metabolite, DDE; and polybrominated diphenyl ethers (PBDEs), which are currently used as flame retardants in textiles, furniture, and other household and office items—accumulate in lake fish. And although recall of eating behaviors over time is imperfect, studies have shown that self-reported histories of the amount of fish consumed correlate with body burdens of PCBs, DDT/DDE, and PBDEs.

McElroy's group has been studying risk factors related to breast cancer as part of an ongoing population-based case–control study. Along with fish consumption, the researchers are also looking at how factors such as physical activity, family history, alcohol consumption, hormone use, and reproductive history impact a woman's chances of developing breast cancer.

The team used telephone interviews of patients newly diagnosed with the disease between 1998 and 2000 to gather data on 1,481 Wisconsin women aged 20–69. A control group of 1,301 randomly selected Wisconsin women with a similar age distribution also was interviewed. The women were asked how often they ate sport-caught fish—and whether any of this fish had been caught in the Great Lakes—over a 12-month period five years before the interviewee's cancer diagnosis or five years before a control's matched reference age.

Consistent with other studies, the survey revealed that the women with breast cancer had gained more weight after age 18 than women without. They were also, as a group, younger at menarche and older at menopause, and were more likely to be older at first full-term pregnancy, consume more alcohol, and have a family history of breast cancer. But women with breast cancer and their age-matched controls were similarly likely to have eaten sport-caught fish, from the Great Lakes as well as from other fishing spots.

Overall, the team found that sport-caught fish consumption was not associated with breast cancer risk in Wisconsin women. But there were two potentially troubling findings specifically regarding premenopausal women under age 40: those who ate any sport-caught fish had almost double the risk of developing breast cancer, and those who ate Great Lakes sport-caught fish had a 74% greater risk.

Although the study makes the link between cancer and consumption of sport-caught fish—a food potentially high in PCBs, DDT/DTE, and PBDEs—no link was drawn to the chemicals themselves. Understanding whether and how these chemicals are involved in breast cancer among women who eat sport-caught fish will require more direct analysis of their concentrations in affected individuals. Still, the authors recommend, it is important to pay attention to the effects of contamination of sport fisheries by these chemicals, especially PBDEs, which are still being manufactured and used in new products. **–Victoria McGovern**

A New Mechanism for Chlorpyrifos?

Implicating Serotonin

Organophosphate pesticides kill insects by allowing the neurotransmitter acetylcholine to build up at nerve endings. This short-circuits the cholinergic system, which governs involuntary processes. Low organophosphate doses given to rats *in utero* are associated with neurodevelopmental effects and impaired behavior in adult animals, and in the past, researchers assumed these adverse effects arose from disruption of the cholinergic system. But recently Justin E. Aldridge and colleagues at Duke University Medical Center found that one organophosphate, chlorpyrifos, appears to affect brain development through other, additional mechanisms, and at doses lower than those that perturb the cholinergic system. Now Aldridge and colleagues report that fetal and newborn rats exposed to chlorpyrifos during particular developmental windows undergo changes in their brain serotonin systems that persist into adulthood, possibly contributing to the neurodevelopmental effects of this particular pesticide [*EHP* 112:148–155].

Chlorpyrifos was once one of the most widely used pesticides in the United States. Due to concerns about its neurologic effects in children, chlorpyrifos was banned from home and garden use in June 2000 under an agreement between the U.S. Environmental Protection Agency and pesticide manufacturers. But it is still used in the United States to protect commercial fruit and vegetable crops, and worldwide it remains one of the most heavily used pesticides.

Aldridge and colleagues injected pregnant rats daily with 1 or 5 milligrams of chlorpyrifos per kilogram body weight (mg/kg) for 3

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days either early (when the brain is first being formed) or late in gestation. These doses bracket the threshold for maternal toxicity and fetal cholinesterase inhibition. They also injected non–previously exposed 1-week-old pups with 1 mg/kg and 2-week-old pups with 5 mg/kg over a 3-day period.

The researchers allowed the young rats and the offspring of the pregnant rats to mature, then harvested the adult aimals and measured biomarkers of serotonin system function in their dissected brains. These biomarkers included a number of serotonin receptors and transporters that the researchers had earlier found to be altered shortly after chlorpyrifos exposure (see *EHP* 111:1736–1743 [2003]).

Although statistically significant effects were seen at all exposure intervals and for both doses, treatments during the late gestational period and the first week after birth—a stage in the rat that parallels the second trimester of human fetal development—had the maximum effects, with increases in receptors and transporters as great as 30–80% above control values in some brain regions. The greatest of these elevations occurred in male rats in the striatum region, which is generally thought to be involved with motor control.

It appears that later in development, the treatment affects males more than females. Other studies of chlorpyrifos's neurodevelopmental effects also have found that sex differences emerged only when exposure occurred late in gestation or in the neonatal period, but those studies did not follow rats to adulthood, nor did they focus on serotonin disruption by chlorpyrifos.

The authors suggest that perturbations in cell differentiation and brain architecture may be one of the contributors to noncholinergic mechanisms of chlorpyrifos-induced neurobehavioral anomalies. Because serotonin is involved in controlling appetite and modulating depression, these results also lend support to the idea that environmental exposures may increase the risk of these problems, according to the authors. **–Rebecca Renner**

The Danger of Extrapolation

Humans and Rodents Differ in Response to PCBs

Although awareness of the extreme toxicity of polychlorinated biphenyls (PCBs) led to their 1976 ban in the United States, these chemicals' virtually indestructible molecular nature and environmental ubiquity make them a continuing serious health threat. Much of what we know about the health effects of PCBs comes from rodent studies, and current thinking in toxicology and risk analysis is based on the assumption that results in animal models will extrapolate to humans. This month, Michelle M. Tabb of the University of California, Irvine, and colleagues report on an investigation comparing human biological response to PCB exposure to that of rodents [***EHP* 112:163–169**]. Their findings indicate there are significant physiological differences between humans and rats that have important implications for risk assessment.

Highly stable and flame-resistant, PCBs have long been used in the manufacture of industrial products such as electrical insulation, machinery lubricants, plastics, wood products, paints, inks, and agricultural pesticides. Although PCBs are no longer made in the United States, their long-term, widespread use and persistence in the environment have made them virtually ubiquitous in soil, water, and air today. PCBs accumulate in animal liver and fat tissue. They disrupt normal hormonal functioning and cause brain and nervous system damage, cancer, and other health problems.

Scientists already knew that when PCBs bind to the pregnane X receptor (PXR) in rodents, the ligand-bound receptor elicits production of enzymes that metabolize PCBs and other contaminants. The current study was a comparative investigation to determine what happens when PCBs bind to the human counterpart to PXR—the steroid and xenobiotic receptor (SXR).

The research design incorporated multiple approaches to evaluate reactions from exposure of human and rat cells to at least 26 different PCBs in separate assays. Activation assays tested the ability of the compounds to activate mRNA transcription of the receptor in transfected cells. The authors used Northern blots to compare the amount of mRNA produced in exposed versus control cells. In another type of test, RNA isolated from exposed cells was converted to cDNA and amplified by QRT-PCR (quantitative real-time reverse transcriptase polymerase chain reaction) to quantify gene expression.

The scientists discovered that the most stable and abundant PCBs found in human tissues activated PXR and induced expression of target genes for metabolizing the toxicants, producing a protective physiological reaction in rodents. In contrast, these same PCBs antagonized SXR, blocking the expression of target genes and inhibiting the human body's ability to physiologically counteract harmful effects of exposure (several less stable PCBs did not antagonize SXR, however). They also found that PCBs were able to increase the amount of a key metabolic enzyme in rat liver cells but not in human liver cells. QRT-PCR analysis showed that treatment with antagonistic PCBs reduced the expression of genes encoding key metabolic enzymes in human cells, confirming the results of the activation assays and Northern blots.

The demonstration that many PCBs block SXR in humans rather than activate it—as previously thought, based on animal models—challenges the assumption that animal models extrapolate to humans. This discovery brings important new insight for development of sound, rational, science-based public policy to protect human health. **–Mary Eubanks**

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Mice are not men. Data showing that humans and rodents differ significantly in their response to PCBs raise doubts about the accuracy of extrapolating from some animal models in toxicology.